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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/629,074 | 07/31/2000 | RONALD G CRYSTAL | 205965 | 5286 |

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

| EXAMINER |
|---|
| BAKER, ANNE MARIE |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 7 |

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/629,074 | CRYSTAL ET AL. | |
| | Examiner | Art Unit | |
| | Anne-Marie Baker | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File



## DETAILED ACTION

The amendment filed August 27, 2001 (Paper No. 6) has been entered. Claims 1, 4, 5, 7, 17, 18, and 22-25 have been amended.

Claims 1-25 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-18 and 22-25 read on a genus of angiopoietin homologous proteins, wherein not a single species of "angiopoietin homologous protein" is described by a specific biochemical or molecular structure such that the recited protein could be envisioned by one skilled in the art at the time of the invention.

The specification as-filed provides a description of angiogenic proteins (e.g. VEGF165) and osteogenic proteins (e.g. BMP-2) that can be used to enhance bone density or formation. Additionally, the specification contemplates using "angiopoetin homologous proteins" (p. 3, lines 11-12) in the method of the

invention. However, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to a genus of potential "angiopoetin homologous proteins" of unspecified molecular structure. What is required is the knowledge in the prior art and/or a complete description within the specification regarding the availability of a representative number of species of "angiopoetin homologous proteins" of defined biochemical or molecular structure exhibiting the disclosed biological functions as contemplated in the specification as-filed.

The written description is not sufficient to support the claimed invention directed to "angiopoetin homologous proteins," because disclosure of no more than a contemplation of "angiopoetin homologous proteins," as in the instant case, is simply a wish to know the identity of any and/or all such proteins having the biological functions as contemplated by the specification and claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of Applicants' effective filing date. Claims reciting unspecified molecular components that must possess the contemplated biological properties, without defining known structures that will function as required, are not in compliance with the written description requirement. Rather, the contemplation of such components is an attempt to preempt the future before it has arrived. *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CAFC 1997). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). Given that a representative number of species of "angiopoetin homologous proteins" are not described in the instant specification, the skilled artisan cannot envision a genus of "angiopoetin homologous proteins" that exhibit

the necessary biological functions, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the specification as-filed. Thus, in view of the reasons set forth above, at the time of the invention, one skilled in the art would not have recognized that Applicant was in possession of a genus of "angiopoetin homologous proteins" that function as required by the claimed invention.

Claims 1-25 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 4-10 of the previous Office Action of Paper No. 5 (mailed 4/24/01), because the specification, while being enabling for administering either 1) a vector encoding FGF or VEGF operably linked to a promoter or 2) a vector encoding FGF or VEGF and a second osteotropic protein each of which is operably linked to a promoter, to a bone progenitor tissue site, a bone fracture site, an osteotomy site, a bone graft, of a bone fusion site, whereby bone density or formation is enhanced, does not reasonably provide enablement for administration of a first and second nucleic acid to a cell associated with bone, whereby bone density or formation is enhanced, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At page 4 of the response, Applicants argue that where the claim recites "region of a bone" the specification defines this term as meaning "in the immediate area of the bone" and further that "region of a bone" includes the bone itself as well as the immediately adjoining area within the bone or in tissues surrounding it (specification at page 2, lines 18-20). Applicants argue that this definition excludes the interpretation that "region of a bone" may be anywhere in the entire body. The Examiner does not agree. Given that the "immediate" area of the bone and the "immediately" adjoining area is not further defined, and

since the entire body surrounds the bones and the specification states that "region of a bone" includes tissues surrounding it (specification at page 2, lines 18-20), the broadest reasonable interpretation for "region of a bone" encompasses the entire body.

At page 4 of the response, with regard to the discussion of systemic delivery of the reagents for purposes of introducing them into the region of a bone, Applicants argue that considerable progress has been made since the articles cited in the Office Action, on viral targeting. Applicants further argue that systemic administration of recombinant adenoviral gene-transfer vectors with bone-specific promoters has been demonstrated to successfully target therapeutic gene expression to cells within bone tissue. Applicants cite the abstract of Matsubara et al. (2001). However, the reference cited is post-filing art and thus the skilled artisan would not have had the benefit of the "considerable progress" on viral targeting to which Applicants refer, nor the benefit of the specific teachings of the Matsubara et al. (2001) reference. Applicants argue that the specification, in combination with the "state of the art as a whole," enables the delivery of the reagents as recited in the pending claims to a region of a bone, both *in vitro* and *in vivo*. However, the relevant "state of the art as a whole" to which Applicants refer is not the state of the art as of 2001, the publication date of the Matsubara et al. reference, but rather the state of the art as of the filing date of the instant application, which is July 31, 2000. The Examiner maintains that the references cited in the Office Action of Paper No. 5 are representative of the state of the art with regard to gene therapy.

At page 5 of the response, Applicants argue that hedgehog proteins can be expected to be osteogenic because published articles suggest that such proteins can enhance bone density or formation. In this regard, Applicants cite Spinella-Jaegle et al. (2001). However, the reference cited is post-filing art and thus the skilled artisan would not have had the benefit of the teachings of the Spinella-Jaegle et al. reference. Furthermore, the reference does not confirm that *in vivo* administration of sonic hedgehog protein correlates

with a therapeutic effect. Thus, the effect of any vector encoding hedgehog proteins, administered *in vivo*, is still unpredictable and the skilled artisan would therefore be required to engage in undue experimentation to produce a therapeutic effect using the claimed method, when the osteogenic protein is a hedgehog protein.

At page 5 of the response, Applicants further point to Kawai et al. (2000) for providing the teaching that endogenous BMP promoters respond to Gli proteins, which are mediators of the hedgehog signal-transduction pathway. However, it is unclear what Applicants are attempting to argue here. The role of Gli proteins discussed, is not sufficient support to indicate that expression of hedgehog proteins near a bone will result in an increase in bone density or formation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18 are indefinite in their recitation of a "cell associated with a region of a bone." Although defined within the specification as being "within the bone ... or in other tissue adjoining the desired region," the definition is further expanded to include any cell that can be "initially away from the region and introduced into it during application of the method." Given the vagueness of this statement, the definition can reasonably be interpreted to encompass administration to any tissue that is within a host. For example, administration to a blood vessel is "administration to a cell associated with a region of bone" because it is near the bone and within the same host and is equivalent to "administration to a cell associated with a region of bone" as claimed. Thus, the metes and bounds of the phrase is not clearly set forth.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bonadio et al. (U.S. Patent No. 5,942,496, 8/24/99), for reasons of record advanced on pages 16-17 of the Office Action of Paper No. 5 (mailed 4/24/01).

Applicants argue that Bonadio does not disclose or suggest the use of any of the factors of claims 1 or 22. However, Claims 19-21 do not recite specific angiogenic or osteogenic factors. Claim 33 of Bonadio et al. specifically recites the use of an adenovirus vector having a DNA insert comprising one or more osteotropic genes.

***Conclusion***

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened

statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600